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Habitual sleep—wake behaviors and lifestyle as predictors of diurnal cortisol patterns in young breast cancer survivors: A longitudinal study

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KEYWORDS
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Lifestyle;
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Physical activity level

Summary
Objective: This study aimed to identify predictors of changes in diurnal cortisol patterns during the 8-month follow up period for young breast cancer survivors. Among the potential predictors were tumor size, lymph node metastasis, changes in sleep problems, habitual time of awakening and bedtime, physical activity levels, body mass index (BMI), and depressive levels across 8 months.
Methods: The participants were 62 breast cancer women who were aged 40 years and below, and had completed active breast cancer treatment. The longitudinal data were collected at four points: baseline assessment (*T*0) and three follow-ups after baseline: *T*1 (in the 2nd month), *T*2 (in the 5th month), and *T*3 (in the 8th month). The participants collected their salivary cortisol at home at six time points: upon waking, 30 and 45 min after waking, and at 1200 h, 1700 h,

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and 2100 h. They also completed several questionnaires: the Medical Outcomes Study Sleep scale; the Beck Depression Inventory-II, physical activity levels on a 10-point scale, time of going to bed, time of awakening, and total sleep hours.
Results: This study found that the main predictors of changes toward flatter diurnal cortisol patterns during the 8-month follow ups were greater tumor sizes, increases of BMI scores, and habitually later times of awakening.
Conclusions: While greater tumor sizes represent biological vulnerability of disruption of cortisol circadian rhythm, maintaining an appropriate BMI and good sleep habits could be a protective factor for normal cortisol regulation, which likely helps to reduce early mortality in young breast cancer survivors.

1. Introduction

The numbers of young women under age 40 being diagnosed with breast cancer are increasing (Cardoso et al., 2012), and the long-term survival outlook is worse in young breast cancer patients than their older counterparts (Klauber-DeMore, 2006; Hartmann et al., 2011; Cardoso et al., 2012). Tumors in young breast cancer patients tend to have higher cancer grade than their older counterparts (Ganz et al., 2002; Sidoni et al., 2003; Klauber-DeMore, 2006). Greater tumor size and greater lymph node metastasis are associated with poor breast cancer prognosis (Klauber-DeMore, 2006; Leij et al., 2012; Cedolini et al., 2014). In addition to biological vulnerability, compared with older breast cancer survivors, younger breast cancer survivors often experience more stress due to having breast cancer at young ages, including the impacts of adjuvant chemotherapy and hormonal therapy on fertility, sexuality, and menopause-related problems (Bloom et al., 2004; Camp-Sorrell, 2009). Cortisol dysregulation due to the cumulative stress is associated with increased incidence and poor progression of breast cancer (Antonova et al., 2011). A flatter diurnal cortisol pattern significantly predicted earlier mortality among metastatic breast cancer survivors (Sephton et al., 2000). Identifying the predictors of diurnal cortisol patterns in young breast cancer patients might help to develop an effective intervention program to prevent earlier mortality. However, the factors associated with diurnal cortisol patterns in young breast cancer patients are not well understood.

Sleep problems, including difficulty with initiating sleep, insufficient sleep duration, and poor sleep quality, are common symptoms experienced by breast cancer survivors (Davidson et al., 2002; Lee et al., 2004; Bower, 2008). Reduced sleep efficiency and more sleep disruption (more frequent waking after sleep onset, more wake episodes, and longer wake episode duration) predict shorter overall survival among women with advanced breast cancer (Palesh et al., 2014). Moreover, the aligned bedtimes (going to bed at preferred bedtime) and being a morning type of chronotypes (earlier wake times and earlier bedtimes) were associated with the longer disease-free interval among breast cancer women with post-menopause status (Hahm et al., 2014). A flatter diurnal cortisol pattern, indicated by higher cortisol levels in the evening and the first half of the night, has been found in insomniacs (Vgontzas et al., 2001). Higher cortisol levels at night are also associated with poor sleep quality in breast cancer patients (Sephton et al., 2000). Flatter diurnal cortisol patterns were correlated with a later time of awakening, shorter total sleep hours, and poorer sleep quality in breast cancer patients (Ho et al., 2013). The relationship between impaired diurnal cortisol pattern and disrupted nocturnal sleep could provide possible explanations for the association of sleep problems with shorter survival in women with metastatic breast cancer (Palesh et al., 2008). However, there is a lack of prospective longitudinal studies to confirm the causal associations of habitual sleep—wake behaviors with diurnal cortisol patterns in breast cancer survivors, especially in young women.

The increases in depressive symptoms during the first year after metastatic breast cancer treatment were correlated with shorter survival among metastatic breast cancer survivors (Giese-Davis et al., 2011). Physical mechanisms for this association are partly attributed to the impacts of depression on hypothalamic—pituitary—adrenal (HPA) function (Sephton et al., 2000). Higher cortisol levels were found to be correlated with more severe depressive levels in patients with metastatic breast cancer (Giese-Davis et al., 2006). Nevertheless, in our previous study (Hsiao et al., 2013) and other studies (Burke et al., 2005; Ho et al., 2013), depressive levels were not associated with diurnal cortisol patterns in the breast cancer patients with the relatively healthy mental profile. It is not clear about the role of depression in influencing diurnal cortisol patterns in young breast cancer patients, who are at higher risk for depression and anxiety (Knobf, 2011).

Factors associated with a healthy lifestyle, including being physically active and maintaining a normal body mass index (BMI), are identified as important predictors of increasing longevity (Moore et al., 2012). Physical activity is regarded as the key protective factor, while higher BMI is identified as a risk factor influencing prognosis in breast cancer patients (Patterson et al., 2010; Protani et al., 2010; Ballard-Barbash et al., 2012). In two review articles, physical activity was correlated with improvements in insulin-like growth factor-I, IGFs, IGFBPs, inflammatory biomarkers, body mass index (BMI), fatigue, depression, and quality of life in cancer survivors (Fong Danniel et al., 2012; Löf et al., 2012). Moreover, these positive effects of physical activity were significantly greater in younger breast cancer survivors. The effects of physical activity and BMI on diurnal cortisol patterns need to be further clarified in younger breast cancer survivors.

In summary, diurnal cortisol patterns could predict survival in young women combating breast cancer. However, to date, there are no studies examining factors associated with diurnal cortisol patterns in young breast cancer survivors. This prospective study with a longitudinal design aimed to clarify which of the factors found to be associated with breast cancer prognosis could predict changes of diurnal cortisol patterns. These factors are tumor size, lymph node metastasis, the changes of sleep and wake variables (sleep problems, habitual wake up time and bedtime), lifestyles (physical activity and BMI), and depressive levels, measured during the 8-month follow up period in young breast cancer

survivors who were aged 40 and below. Identifications of the predictors of diurnal cortisol patterns could help to develop an effective intervention to maximize survivorship of young women after treatment for breast cancer. Moreover, understanding of the roles of such predictors as they relate to diurnal cortisol patterns may lead to elucidation of potential biological mechanisms behind their impacts on breast cancer prognosis.

2. Methods

2.1. Participants

Participants were recruited from the outpatient department for breast center at two general hospitals and participated in our supportive care program with 8-months of follow up: baseline assessment (*T*0) and three follow-ups after baseline: *T*1 (in the 2nd month), *T*2 (in the 5th month), and *T*3 (in the 8th month). The inclusion criteria of recruitment were women with breast cancer, aged 40 and below, and completion of all active cancer treatments (surgery, chemotherapy, or/and radiotherapy). Participants were excluded if they had a history of other types of cancers or if they had adrenal function disorders such as Cushing syndrome, Addison's disease, an adrenal tumor, or a pituitary tumor. Fig. 1 is the flowchart of subject participation through the 8-month follow-up. A total of 131 participants who met the inclusion criteria were recruited but 69 declined to participate. The main reasons for refusing to participate in this study were no time to join in the supportive care program or not time to complete the 8-month follow-up measurements. The total numbers of participants were 62 at *T*0 (baseline). The numbers of participants dropping out were 0 at *T*0, 8 at *T*1, 1 at *T*2, and 0 at *T*3. There were no significant differences in the demographic and medical variables (cancer and treatment variables) between the participants who completed all measurement tests and those who dropped out of the study.

As indicated in Table 1, the mean age of the subjects was 35.3 years old with a range of ages from 26 to 40 years. Marital status in over an half of the subjects was single. The majority of subjects completed education through a bachelor's degree or post graduate levels, and most of the subjects had a job and stated religious belief. In regard to cancer and treatment variables, the majority of the subjects were diagnosed with stage 0 to II breast cancer. For most subjects, the cancer was estrogen and progesterone receptor positive, while Her-2 neu positives occurred in a few subjects. Family history of cancer was found in over half of the subjects. All subjects received surgery and most subjects received chemotherapy, radiotherapy, and hormone therapy. A few subjects received target therapy (trastuzumab). The mean durations between completing active treatments and participating in this study were 1.73 years with a range of 6 days to 5.99 years.

2.2. Measures

After being informed and instructed about the study, the participants collected saliva for measurement of cortisol responses using neutral cotton salivette tubes (Sarstedt, Germany) in their homes at six time points: upon waking, 30, and 45 min after waking, and at 1200 h, 1700 h, and 2100 h. Each participant collected saliva samples at all time points on a single day. The participants were told not to brush their teeth before completing the first salivary sampling of the day and not to eat before the first three collections had been completed. For the remaining three samples, participants were asked not to eat during the 30 min immediately before they collected each sample. Except for the above restrictions, participants followed their normal, daily routines on the sample collection day. For each time point, after completing the saliva collection, the participants were asked about their self-perceptions of sleep quality, physical activity levels, perceived physical health status, perceived stress levels on a 10-point scale (5 indicating level or condition same as usual, the day relative to other recent days; less than five indicating lower than usual; more than 5 indicating higher than usual) and they also provided the information about their usual time of going to bed and the time they went to bed the last night of collecting saliva, and usual time of awakening and time of awakening in the morning of collecting saliva, their smoking, alcohol and coffee-drinking habits, and status of menstrual cycle. Their height and weight were used to calculate BMI (kg/m^2) for calculating an index of adiposity.

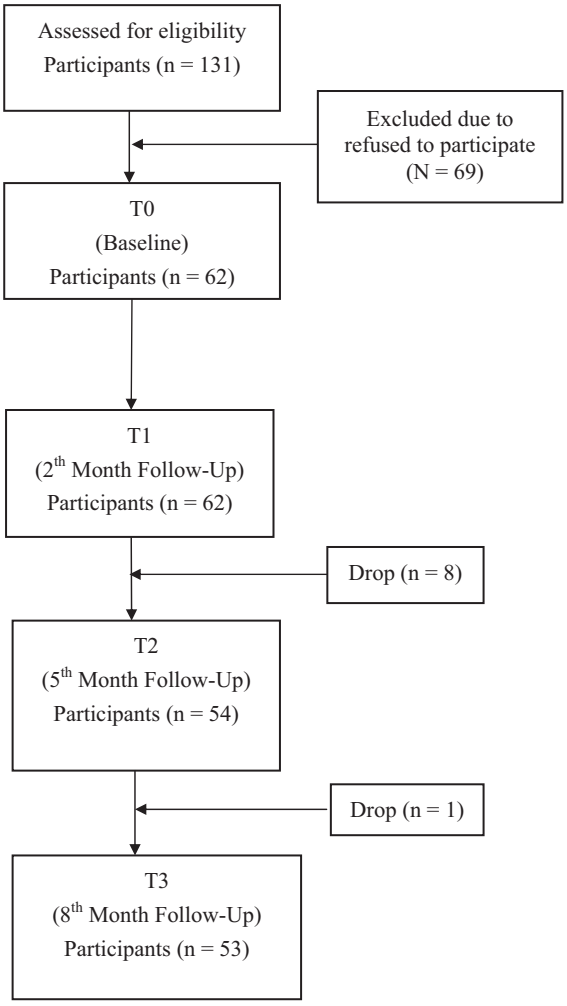

Figure 1 The flowchart of subject participation through the 8-month follow up.

The 12-item MOS sleep scale (Spritzer and Hays, 2003) contains six subscales: sleep disturbance, snoring, shortness of breath or headache during sleep, sleep adequacy, sleep somnolence, and sleep quantity. Except for sleep quantity, recorded as 0—24 h, the rest of the subscales were combined into a nine-item sleep problem index, presented as a composite index of sleep disturbance, snoring, shortness

Table 1 Sociodemographic and medical characteristics of the subjects ($n = 62$).

Variables	
Age (Mean + SD), years	35.3 ± 3.2
Marital status	
Single/cohabiting, %	53.2/46.8
Education	
College graduate and above/high school graduate and below, %	91.9/8.1
Working status	
Employed/unemployed, %	75.8/24.2
Religion, yes/no	74.2/25.8
Family history of cancer	
Yes/no, %	54.8/45.2
Cancer stage	
0/I/II/III, %	13.3/40.0/36.7/10.0
Tumor size (Mean + SD), cm	2.2 ± 1.8
Metastasis	
Yes/no, %	25.8/74.2
Estrogen receptor (ER)	
Positive/negative, %	86.4/13.6
Progesterone receptor PR	
Positive/negative, %	70.9/29.1
Her-2 neu	
Positive/negative, %	18.0/82.0
Chemotherapy	
Yes/No, %	62.9/37.1
Radiotherapy	
Yes/no, %	69.4/30.6
Target therapy	
Yes/no, %	11.3/88.7
Hormone therapy	
Yes/no, %	80.6/19.4
Length after completing treatment, (Mean + SD), years	1.7 ± 1.6

of breath or headache during sleep, sleep adequacy, and sleep somnolence, and scored on a scale of 0—100. Higher scores on the sleep problem index indicate higher levels of sleep problems. Scores on the 21-item BDI-II scale (Beck et al., 1961) range from 0 to 63. Cutoff values of 15 and 20, respectively, were used to define mild and moderate-to-severe levels of depressive symptoms. Higher scores for BDI-II indicate more severe levels of depression.

2.3. Procedures

After the study was approved by the hospital institution review board, the researcher's assistant explained the purposes, procedures, risks, and benefits of the study to the potential participants. After the participants gave their written consent, they received the self-report questionnaires, the neutral cotton salivette tubes (Sarstedt, Germany), and instructions for collecting saliva at home. After completing the saliva collection, they sent the samples, along with completed self-report questionnaires, by frozen courier service to our office where the samples were stored at −17°C. Noncompliance with the saliva sampling procedure among patients should be minimal if the procedures for collecting samples are clearly explained to participants (Remillard et al., 1993). Accordingly, in addition to explaining clearly about the sampling procedure both verbally and in writing, to verify adherence to saliva collection protocol, participants were asked to fill in the actual time of collection of each saliva sample on a time sheet that also provided sampling instructions and a list of the desired sampling times. Only two participants collected the samples at the incorrect time at the *T*0 (baseline test) and they were then asked to collect the samples again within 3 days. Therefore, all samples were collected completely. A commercially available immunoassay (IBL, Hamburg, Germany) was used to measure the level of free cortisol. Inter-assay and intra-assay variation was less than 10%. The self-report questionnaires and the saliva kits for the follow-up tests were sent to the participants through the mail for repeating the same collection procedures.

2.4. Data analysis

2.4.1. Analyzing diurnal cortisol patterns

Steeper diurnal cortisol patterns are characterized by a normal descending profile from high morning cortisol levels to lower evening cortisol levels (Sephton et al., 2000). On the other hand, a flatter diurnal cortisol pattern does not show descending cortisol levels as the day progresses. There were a number of steps to analyze diurnal cortisol patterns: salivary cortisol levels (nmol/l) skewed positively, so we used the natural logarithm to transform the raw cortisol levels and yield an unskewed distribution for further analysis. Diurnal cortisol slopes were determined based on cortisol levels collected at the six time points: upon waking, 30 and 45 min after waking, and at 1200 h, 1700 h, and 2100 h. β values for diurnal cortisol slopes (log nmol/l per hour) were calculated based on a regression of the log-transformed mean (standard deviation) cortisol levels (nmol/l) from at six measuring times. Steeper slopes, which show cortisol levels declining more rapidly, are indicated by smaller β values for the slope of the regression while flatter slopes are indicated by larger β values, which show slower declines (Sephton et al., 2000).

2.4.2. Examining the changed means for the major variables over the 8 months

The generalized estimating equation (GEE) was used to examine whether significant change occurred in the means of the main variables from the baseline levels (*T*0) across the 2nd (*T*1), 5th (*T*2), and 8th months (*T*3). The χ^2 value generated by the statistic test of within-subject effects showed significant values for the change in means by time for the main variables of diurnal cortisol slopes, BMI, physical activity levels, BDI-II depressive symptoms, time of going to bed night before collecting saliva and normally as sleep habit (hours), and time of awakening the morning of collecting saliva and normally as sleep habit (hours), and sleep problems index.

To further analyze how many percent of the patients had increases, decreases, or no change for each predictor variable, we calculated individual slope for each predictor by constructing across assessments from the baseline data and all follow-up tests and regressed across time using months as the unit of time. The slope values 0 indicated no change from *T*0 to *T*3, the positive slope (the values greater than 0) showed the increases of the scores from *T*0 to *T*3, and the negative slope (the values less than 0) revealed the decreases of the scores from *T*0 to *T*3.

2.4.3. Analysis of the main predictors of the changes in diurnal cortisol slopes in generalized estimating equations (GEE) models during the 8-month follow ups

Generalized estimating equation (GEE) analyses were used to identify the main predictors for the changes of diurnal cortisol patterns during the 8-month follow ups. The data of diurnal cortisol slopes from all time points were used in GEE analysis. A linear pattern of change was assumed to analyze that diurnal cortisol slopes became steeper or flatter patterns across 8 months (larger or smaller β values for the slope of the regression). We investigated the associations of the changes in the potential predictors with the changes in diurnal cortisol patterns during the 8-month follow ups. AR-1 working correlation structure was applied to adjust for within-subject correlation by modeling of changes over time rather absolute values at different time points. Time was modeled as both a categorical variable (baseline, the 2nd month, the 5th month, and the 8th month) and a continuous variable when the changes in diurnal cortisol slopes over 8 months were analyzed. The potential predictors were centered at their mean values in the GEE model to obtain interpretable regression coefficients. These potential predictors were: tumor sizes, lymph nodes metastasis, physical activity levels, BMI scores, sleep problems index; habitual time of going to bed and time of awakening, and BDI-II depressive symptoms. There were the positive significant correlations between time of going to bed night before collection of saliva and habitual bedtime ($r = 0.802$, $p < 0.001$), between time of awakening morning of collecting saliva and habitual time of awakening ($r = 0.752$, $p < 0.001$). Therefore, time of waking/going to bed on (before) day of saliva collection is included in GEE model as a covariate. Estimated regression coefficients are presented with beta coefficient values, standard error, 95% confidence intervals and p-values. All statistical tests performed were two-sided and considered significant at p-value <0.05. The data analyses were performed using IBM SPSS statistics 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Change in means of the diurnal cortisol slopes and the potential predictors over 8 months

Table 2 indicates the means (standard deviation) of main variables from *T*0 to *T*3 during the 8-month follow up. GEE test showed that there were significant changes of diurnal cortisol slopes across the 8 months ($\chi^2 = 16.67$, $p = 0.001$). The findings indicated that, compared with the baseline, diurnal cortisol slopes at the 8th month were steeper (Beta = −0.28, Std. Error = 0.08, $\chi^2 = 9.89$, $p = 0.002$). There were also significant decreases in the BDI-II depressive symptoms across 8 months ($\chi^2 = 10.33$, $p = 0.016$). The scores of BDI-II depressive symptoms were significantly lower than baseline at the 5th month (Beta = −2.50, Std. Error = 0.81, $\chi^2 = 9.49$, $p = 0.002$) and at the 8th month (Beta = −1.96, std. error = 0.74, $\chi^2 = 6.97$, $p = 0.008$). However, there were no significant changes from baseline in BMI, physical activity levels, time of going to bed night before collecting saliva and normally as sleep habit (hours), time of awakening the morning of collecting saliva and normally as sleep habit (hours), and sleep problems index ($p > 0.05$) during the 8-month follow up period.

About how many percent of the participants had increases, decreases, or no change for each predictor variable during the 8-month follow ups, the results of the individual slope for each predictor indicated that more participants experienced the increases of BMI scores (54.5%) than the decreases (41.8%) or no change (3.6%) of BMI scores. More participants had the later habitual time of going to bed (54.5%) than going to bed earlier (36.4%) or no change of bedtime (9.1%) across 8 months. More participants experienced earlier habitual wake up time (54.5%) than those who woke up later (34.5%) and no change of time of awakening (10.9%) during the 8-month follow ups. Majority of the participants (61.8%) experienced the decreases of BDI-II scores than those with increased BDI-II scores (38.2%) across 8 months. More participants had the decreased scores of sleep problem index (54.5%) than the increased scores (45.5%). There were the equal numbers of increases (45.5%) and decreases (45.5%) of physical activity levels while the small numbers remained no change (9.1%) f physical activity levels during the 8-month follow ups.

3.2. Predictors of changes of diurnal cortisol slopes over 8-month follow up

As depicted in Table 3, GEE analysis indicated that, in the multivariate regression model, tumor sizes, BMI, and time of awakening normally as a sleep habit were significantly associated with the changes of diurnal cortisol slopes during the 8-month follow ups. The greater tumor sizes and increases of BMI scores over 8 months were positively correlated with changes toward flatter diurnal cortisol slopes ($\beta = 0.04$, SE = 0.01, $p = 0.01$; $\beta = 0.06$, SE = 0.01, $p < 0.001$). A persistently later time of awakening normally as a sleep habit over the 8 months predicted flatter diurnal cortisol patterns ($\beta = 0.12$, SE = 0.04, $p = 0.006$). However, lymph nodes metastatic status ($\beta = -0.06$, SE = 0.06, $p = 0.302$), physical activity levels ($\beta = -0.01$, SE = 0.01, $p = 0.384$), time of going to bed normally as a sleep habit ($\beta = -0.006$, SE = 0.04, $p = 0.888$), sleep problem index ($\beta = -0.002$, SE = 0.002, $p = 0.457$), and BDI-II depressive symptoms ($\beta = 0.003$, SE = 0.004, $p = 0.512$) were not associated with diurnal cortisol patterns during the 8-month follow up.

4. Discussion

This study found that the main predictors of changes toward flatter diurnal cortisol patterns during the 8-month follow up were greater tumor sizes, increasing BMI score over the course of the study, and a habitually later time of awakening. Greater tumor sizes could be regarded as a biologically vulnerable factor of cortisol dysregulation, maintaining good BMI and healthy sleep habits such as an earlier time of awakening could be regarded as a protective factor for normal cortisol regulation in young breast cancer survivors. According to the previous finding that flatter diurnal cortisol patterns correlated with earlier mortality among metastatic breast cancer survivors (Sephton et al., 2000), enhancing healthy lifestyles and good sleep habits may improve cortisol responses and thus help protect young breast survivors from earlier mortality.

Greater tumor sizes are an important factor associated with poor breast cancer prognosis in young breast cancer patients (Klauber-DeMore, 2005, 2006) with multicentric and multifocal breast cancer (Rezo et al., 2011). The tumor characteristics in young breast cancer patients tend to be more aggressive than their older counterparts (Ganz et al., 2002; Klauber-DeMore, 2006; Sidoni et al., 2003). Our results showed that the greater tumor sizes predicted flatter diurnal

Table 2 The mean and standard deviations (SD) of main variables at four measurement times during 8 months follow up.

	*T*0	*T*1	*T*2	*T*3	Statistical analysis
					χ^2=, *p*=
Diurnal cortisol slope (log nmol/l per hour) (Mean (SD))	−1.13	−1.15	−1.15	−1.41	$\chi^2 = 16.67$
	(0.56)	(0.51)	(0.39)	(0.47)	$p = 0.001^{**}$
BMI (Mean (SD))	21.12	21.19	21.26	21.41	$\chi^2 = 4.96$
	(2.12)	(2.13)	(2.16)	(2.30)	$p = 0.174$
Physical activity (Mean (SD))	4.94	4.63	4.56	5.11	$\chi^2 = 5.08$
	(1.12)	(1.64)	(1.87)	(1.35)	$p = 0.166$
Time of going to bed night before collecting saliva (hours)	23.99	23.97	23.87	23.83	$\chi^2 = 1.33$
	(0.17)	(0.15)	(0.13)	(0.15)	$p = 0.720$
Time of going to bed normally (hours)	23.79	23.58	23.69	23.65	$\chi^2 = 6.86$
	(0.15)	(0.15)	(0.12)	(0.14)	$p = 0.076$
Time of awakening morning of collecting saliva (hours)	7.22	7.21	7.15	7.11	$\chi^2 = 0.62$
	(0.19)	(0.16)	(0.17)	(0.15)	$p = 0.891$
Time of awakening normally (hours)	7.47	7.38	7.26	7.30	$\chi^2 = 2.68$
	(0.18)	(0.16)	(0.14)	(0.16)	$p = 0.443$
Sleep problems index	30.53	30.19	28.78	29.49	$\chi^2 = 3.97$
	(12.83)	(13.18)	(12.30)	(12.13)	$p = 0.265$
BDI-II depressive symptoms	9.59	8.14	7.11	7.52	$\chi^2 = 10.33$
	(7.07)	(7.61)	(6.18)	(6.07)	$p = 0.016^{*}$

* $p < 0.05$.
** $p < 0.01$.

cortisol patterns over 8 months during the post-treatment survivorship stage. The results suggest that the association of tumor sizes with cortisol dysregulations might illustrate possible physical mechanisms for the impacts of tumor biology on cancer progression in young breast cancer patients (Cardoso et al., 2012; Hartmann et al., 2011; Klauber-DeMore, 2006).

This study identified that the increases of BMI scores over the 8 months were associated with the changes toward flatter diurnal cortisol patterns. Review studies indicated that higher BMI is consistently identified as a major risk factor for breast cancer recurrence and decreased survival (Patterson et al., 2010; Protani et al., 2010). Moreover, the potential biological mechanisms of the associations of obesity with poor breast cancer prognosis are related to the impacts of excess adiposity on increased levels of estrogens, insulin, leptin, and pro-inflammatory cytokines, which enhance the changes in cellular environment that favor tumor formation and proliferation. A flatter diurnal cortisol pattern was associated with a higher metabolic risk in blood pressure, plasma

Table 3 Predictors of the changes in diurnal cortisol patterns over 8 months in multivariate GEE model.

Variables	Beta	SE	95% CI lower	95% CI upper	Wald χ^2	*p*
Tumor sizes	0.04	0.01	0.01	0.07	6.66	0.010*
Lymph nodes metastasis						
Yes	−0.06	0.06	−0.19	0.06	1.06	0.302
No†	0					
BMI	0.06	0.01	0.03	0.09	14.50	<0.001***
Physical activity	−0.01	0.01	−0.03	0.01	0.75	0.384
Time of going to bed night before collecting saliva (hours)	0.06	0.03	−0.005	0.12	3.28	0.070
Time of going to bed normally (hours)	−0.006	0.04	−0.09	0.07	0.02	0.888
Time of awakening morning of collecting saliva (hours)	0.007	0.04	−0.07	0.09	0.03	0.859
Time of awakening normally (hours)	0.12	0.04	0.03	0.21	7.49	0.006**
Sleep problems index	−0.002	0.002	−0.006	0.003	0.51	0.475
BDI-II depressive symptoms	0.003	0.004	−0.005	0.01	0.42	0.512

Working correlation matrix structure: AR(1).
Goodness of fit: quasi likelihood under independence model criterion (QIC) = 61.206.
Corrected quasi likelihood under independence model criterion (QICC) = 62.602.
† =0 as reference group.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

glucose, lipid regulation, ghrelin, and adipocyte-secreted hormones (leptin and adiponectin) (Corbalan-Tutau et al., 2014). In our study, the increases of BMI scores over 8 months as a predictor of the changes toward flatter diurnal cortisol patterns suggests that overweight and obesity more likely result in dysregulation of cortisol responses than healthy weight. Accordingly, the impacts of obesity on poor breast cancer prognosis might be through its influence on cortisol circadian dysregulations in young breast cancer survivors.

The previous study found that BMI was positively related to tumor sizes at diagnosis (Eichholzer et al., 2013) and hormone receptor-positive tumors in younger breast cancer patients (Yang et al., 2011). Differently, in our study of young breast cancer survivors, BMI scores at the post-treatment survivorship stage were not significantly associated with cancer characteristics (tumor sizes, positive or negative status of estrogen and progesterone receptors, Her-2 neu) and with/without menstrual cycle ($p > 0.05$) but were significantly negatively correlated with self-perceived physical activity levels ($r = -0.26$, $p = 0.036$). The results suggest that increased BMI during the post-treatment survivorship stage was unlikely to be directly related to tumor characteristics, but rather was impacted by a healthy lifestyle such as physical activity. Physical activity could be helpful to maintain good BMI in young breast cancer survivors. The review study (Patterson et al., 2010) revealed that, while adiposity was associated with increased risk for mortality, physical activity was related to decreased risk of mortality.

In this study, sleep problem index scores did not predict diurnal cortisol patterns. This might be because the mean scores of the sleep problem index across 8 months were below 31 (score ranges 0—100), which indicated that participants did not generally have significant sleep problems such as snoring, shortness of breath or headache during sleep, sleep inadequacy, or somnolence. Nevertheless, this study found that one specific poor sleep habit (persistently later time of awakening) over 8 months predicted flatter diurnal cortisol patterns in young breast cancer survivors. To the best of our knowledge, up to date there is no clear definition of when to wake up as the later time of awakening. In our sample, average of wake up time normally around 730 h. We further examine the role of time of awakening before/after 730 h as the predictor of diurnal cortisol patterns in GEE multivariate model. The persistently waking up at 730 h after over the 8 months was 1.176 times more likely to have flatter diurnal cortisol patterns when it was compared to waking up before at 730 h ($\beta = 0.162$, SE = 0.082, $p = 0.048$). Our findings suggest that persistently waking up later than 730 h could be regarded as the poor sleep habit. Later time of awakening was considered as a perpetuating factors contributing to the negative patterns of circadian rhythms in cancer patients (Lee et al., 2004; Thomas et al., 2008). The previous study (Ho et al., 2013) also found that flatter diurnal cortisol patterns were associated with a later time of awakening. One review study (Fries et al., 2009) indicated that a later time of awakening was associated with lower cortisol levels at time of awakening and lower cortisol awakening responses (CAR) in healthy people (Stetler and Miller, 2005; Wilhelm et al., 2007). When cortisol levels at time of awakening are lower than expected secretion in the morning, the situation contributes to a flatter diurnal cortisol pattern. A later time of awakening is often related to maladaptive sleep habits such as spending more time in bed, which influence sleep—wake cycle and subsequently increase the risk of long-term sleep problems in the general population (Savard and Morin, 2001). The previous studies (Savard et al., 2005; Porter, 2012) found that the impacts of cognitive behavioral interventions on stable sleep behaviors are correlated with better cortisol responses. While the meta-analysis study (Megdal et al., 2005) focused on the impacts of night shift work on the risk of breast cancer, our findings suggest that the persistently poor sleep habit of a later time of awakening disrupts the internal circadian timing system, which contributes to the long-term dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in young breast cancer survivors.

In this study, the unexpected lack of correlation between diurnal cortisol patterns and depression might be because the scores of depression in this population were often below cut-off scores for clinical diagnosis. Similar to previous studies (Burke et al., 2005; Ho et al., 2013; Hsiao et al., 2013), the associations of flatter diurnal cortisol patterns with depression did not occur in healthy people with relatively healthy mental status.

5. Conclusion

These results suggest that greater tumor sizes, increased BMI scores, and persistently later time of awakening over the course of 8 months are the risk factors associated with the changes toward flatter diurnal cortisol patterns in young breast cancer survivors. The results demonstrate that, besides the cancer's biological vulnerability, a healthy lifestyle including maintaining appropriate BMI and good sleep habits could be protective of positive cortisol regulation, which might help to reduce early mortality in young breast survivors. Limitations influencing the ability of this study to make generalized statements based on the results include the facts that most of the breast cancer survivors in this sample were in early cancer stages, were not in metastasis, had cancer characteristics positive for estrogen and progesterone receptors and negative for Her-2 neu, and did not have significant depressive symptoms or sleep problems. Nevertheless, implications of this study for management of follow up care for young breast cancer survivors suggest that in addition to an emphasis on hormone therapy and psychosocial care (Freedman and Partridge, 2013), maintaining good BMI and sleep habits, especially an earlier time of awakening, could be helpful to prevent a poor cancer prognosis.

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Conflict of interest

All authors of this study declare that we all have no conflicts of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the work submitted that could inappropriately influence, or be perceived to influence, our work.

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